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1 Objectives:

2 This study identified the difference in energy expenditure and substrate
3 utilization of patients during and upon liberation from mechanical ventilation.

4
5 Methods:

6 Patients under intensive care who were diagnosed with septic shock and
7 mechanical ventilation-dependent were recruited. Indirect calorimetry
8 measurements were performed during and upon liberation from mechanical
9 ventilation.

10
11 Results:

12 Thirty-five patients were recruited (20 males and 15 females; mean age 69 ± 10
13 years). Measured energy expenditures during ventilation and upon liberation
14 were $2090 \pm 489 \text{ kcal} \cdot \text{d}^{-1}$ and $1910 \pm 579 \text{ kcal} \cdot \text{d}^{-1}$, respectively ($p < 0.05$).
15 Energy intake was provided at $1148 \pm 495 \text{ kcal} \cdot \text{d}^{-1}$ and differed significantly
16 from all measured energy expenditures ($p < 0.05$). Mean carbohydrate
17 utilization was $0.17 \pm 0.09 \text{ g} \cdot \text{min}^{-1}$ when patients were on mechanical
18 ventilation compared to $0.14 \pm 0.08 \text{ g} \cdot \text{min}^{-1}$ upon liberation ($p > 0.05$). Mean
19 lipid oxidation was $0.08 \pm 0.05 \text{ g} \cdot \text{min}^{-1}$ during and $0.09 \pm 0.07 \text{ g} \cdot \text{min}^{-1}$ upon
20 liberation from mechanical ventilation ($p > 0.05$).

21
22 Conclusions:

23 Measured energy expenditure was higher during than upon liberation from
24 mechanical ventilation. This could be the increase in work of breathing from
25 the continuous positive pressure support, repeated weaning cycles from
26 mechanical ventilation and/or the asynchronization between patients'
27 respiration and ventilator support. Future studies should examine whether
28 more appropriately matching energy expenditure with energy intake would
29 promote positive health outcomes.

30

31 **Introduction**

32 Critically ill populations are especially susceptible to malnutrition due to their
33 hypermetabolic state combined with suboptimal nutrition support^{1,43}. Sepsis is
34 a complex and progressive physiological stress response to infection among
35 patients, involving multiple organs and high mortality rate². The related stress
36 response changes energy expenditure and can differ during various stages of
37 sepsis (i.e. highest in complicated sepsis but similar to healthy individuals in
38 septic shock^{5,6}).

39

40 Energy expenditure is positively related to the duration of sepsis⁷ and
41 substrate utilization can also be altered during such critical illness.^{8,10}. In
42 addition to the clinical condition *per se*, treatment with mechanical ventilation
43 support has the capacity to increase a patient's energy expenditure⁴⁰. This
44 observation is particularly apparent amongst patients on partial pressure
45 support, which requires increased work of breathing to reach the sensitivity
46 threshold that triggers the ventilator to complete the respiration³⁶.

47

48 In this study, the focus was the change in energy expenditure during
49 *liberation*, defined as cessation of any pressure support from the ventilator. A
50 common technique in intensive care unit is to gradually liberate patients from
51 mechanical ventilation using a repeated “work” and “rest” cycle. This cycle
52 allows respiratory muscles to rest adequately with partial pressure support
53 from the ventilator so that atrophied respiratory muscles may be strengthened
54 and self-breathing can begin in a less fatigue state³⁰. However, there is
55 evidence that energy expenditure may gradually elevate through each “work”
56 and “rest” cycle³⁰. Based on the available evidence, we hypothesized that
57 energy expenditure would vary over time in the process of weaning from
58 mechanical ventilation to the fully liberated state when pressure support from
59 the ventilator is entirely withdrawn.

60

61 **I. Methodology**

62 This study complied with the 2013 version of the Declaration of Helsinki and
63 approval was obtained from the ethics committee of the Kowloon East Cluster
64 hospitals, Hospital Authority, Hong Kong SAR (approval reference: KC/KE-
65 09-0107/ER-2).

66 *Participant Recruitment*

67 Patients aged 18 and above who were admitted into the intensive care unit
68 with initial diagnosis of septic shock and mechanical ventilation dependent
69 were recruited. Patients must have been hemodynamically stable at the time
70 of indirect calorimetry measurement. Patients with significant post-operative
71 bleeding, major pulmonary complications, under isolation protocol and/or with
72 comfort care directives were excluded.

73

74 The stature of patients was measured from the crown to the bottom of their
75 feet in the supine position using a measuring tape. Body mass was obtained
76 from either past records, next of kin or by calculating the ideal body weight.
77 Length of stay, duration on ventilator and APACHEII²⁸ were collected (Table
78 1).

79 *Indirect Calorimetry*

80 CCM Express²⁹ was selected for indirect calorimetric measurement in this
81 study. The connecting circuitry is composed of a DirectConnect_{TM} volume-
82 measuring flow sensor and umbilical, which connects to the terminal and all
83 expiratory gas from patients directed through DirectConnect_{TM}. A face-mask
84 and canopy were not options for measuring devices as patients had either
85 tracheostomy or endotracheal tube insertion.

86

87 A system calibration on CCM Express is performed according to American
88 Thoracic Society recommendation using a 3-liter syringe for volume
89 calibration. A designated volume of air is introduced by the syringe into the

90 flow sensor several times at different flow rates in three separate trials. CCM
91 Express utilizes an external gas calibration device for calibration with two
92 gases; reference gas (21% of gas volume oxygen and nitrogen typical of
93 atmospheric composition) and calibration gas (12% oxygen, 5% carbon
94 dioxide and nitrogen similar to atmospheric composition). An auto-calibration
95 which includes correcting continuous bias flow was also performed. Bias flow
96 minimizes the work of breathing by allowing the patient to tap into a
97 continuous gas flow rather than initiate flow through a delivery circuit. The
98 system is able to differentiate between gas delivery to the patient's lungs and
99 gas continuously flowing through the circuit³³. Measurements from indirect
100 calorimetry were deemed valid once steady state can be achieved by the
101 patients²⁰.

102 *Nutrition support*

103 Nutrition support was the provision of formulated enteral or parenteral
104 nutrients to appropriate patients for maintaining or restoring nutrition
105 balance²¹. It was provided to this cohort through either tube feedings or oral
106 diets. The route of tube feedings was either nasal gastric, nasal jejunal tube or
107 jejunostomy. The rate of feeding was controlled by electric feeding pumps
108 that dispensed feeding continuously at a fixed rate. All feeding regimens
109 remained unchanged pre- and post-indirect calorimetry measurement. Tube
110 feedings were withheld 4 hours prior to indirect calorimetry measurement in
111 order to minimize the influence from thermogenesis of food.

112 *Patients Care-Specific Measurement Protocols*

113 Indirect calorimetry measurements only commenced after 90 minutes
114 following procedures such as bathing, turning, physiotherapy, change of
115 ventilator setting, change of dosage of sedatives or inotropes or hemodialysis
116 with possibility of excess accumulation of bicarbonate in the blood.
117 Physicians also gradually tapered the level of sedation with a decreased level
118 of ventilator support. Energy expenditure was measured once during a stable

119 ventilator setting (Pre-MEE). It was measured again after 90 minutes of
120 liberation or cessation of pressure support from mechanical ventilation (Post-
121 MEE). The results were deemed valid when the patient did not require
122 reintubation for at least the following 12 hours.

123 *Automatic Tube Compensation Protocol*

124 Patients were often mechanically ventilated either by tracheostomy or
125 endotracheal-tube to create an external airway to the lungs. The endotracheal-
126 tube was used for short-term ventilator support and removed when the patients
127 are able to wean themselves off mechanical ventilation. The direct connection
128 of the endotracheal tube to the circuitry of the indirect calorimetry for
129 measurement is then no longer available. Hence, a specific protocol was
130 developed to accommodate the measurement for patients who utilized
131 endotracheal tube for mechanical ventilation. Automatic Tube Compensation
132 (ATC) mode in mechanical ventilators relieves the pressure imposed by the
133 endotracheal-tube inside the airway and its subsequent impact on work of
134 breathing. This ATC protocol allowed the cohort to retain the endotracheal
135 tube for connecting to the indirect calorimeter circuitry. The setting of the
136 ventilator was adjusted to supply only oxygen without pressure support to
137 simulate self-breathing¹⁶. Indirect calorimetric measurements were performed
138 after 90 minutes of cessation of pressure support for proper acclimatization
139 and patients were then extubated after the measurement. Data were again
140 deemed valid when patients did not require reintubation for the next 12 hours.

141 *Modification In Resting Energy Expenditure and Substrate Utilization* 142 *Calculation*

143 The indirect calorimeter automatically determined the concentration of oxygen
144 consumed and carbon dioxide produced by patients and data were converted
145 into energy expenditure ($\text{kcal}\cdot\text{d}^{-1}$)¹⁴ with carbohydrate utilization and lipid
146 oxidation were then determined based on the respiratory exchange ratio¹³.
147 Urinary nitrogen was not collected in this cohort because of practical

148 limitations in laboratory capacity. Research indicated that there was only 1%
 149 of error for every 12.3% of total calories metabolized from protein and thus,
 150 the equation could be simplified by excluding urinary nitrogen¹⁴.

$$151 \quad (3.914 \cdot \dot{V}O_2 \text{ L min}^{-1}) + (1.106 \cdot \dot{V}CO_2 \text{ L min}^{-1})(2.17 \cdot n \text{ gm min}^{-1}) \cdot 1400 \text{ min day}^{-1}$$

152 ***Statistical Analysis***

153 All statistical analysis was performed by EXCEL 2010 version 12.0
 154 (Microsoft Inc.). Mean values and standard deviation were used to express
 155 descriptive statistics. Paired-t tests were used to examine mean differences
 156 between during and following liberation from mechanical ventilation in
 157 energy expenditure (pre-MEE vs post-MEE), actual energy consumption
 158 (KCAL), oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and
 159 substrate oxidation. Spearman's correlation coefficient was used to assess the
 160 relationship among variables and significance accepted at $p \leq 0.05$. Only
 161 correlations with 'good' agreement (i.e. $r \geq 0.7$) were reported. Variability of
 162 data was expressed as standard deviation.

163

164 **Results**

165 There were originally 37 patients in the cohort and 2 patients terminated their
 166 indirect calorimetry measurements prematurely due to post-operative seizures,
 167 persistent restlessness and/or irritation during measurement. Thirty-three
 168 patients received actual calories from tube feeding, one patient did not receive
 169 any nutrition support and the remaining one was on oral diet during entire
 170 study period. Disease conditions of the cohort included:

- 171 • Central Nervous System (CNS) Infection
- 172 • Status epilepticus with sepsis
- 173 • Acute cholecystitis
- 174 • Type I respiratory failure and septic shock
- 175 • Herpes encephalitis

- 176 • Hospital-acquired pneumonia
- 177 • Pancreatitis and septic shock
- 178 • Urosepsis
- 179 • Perforated Peptic Ulcer
- 180 • Community-acquired pneumonia
- 181 • Parapharyngeal abscess and pneumonia
- 182 • Retropharyngeal abscess
- 183 • Liver abscess
- 184 • Methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia
- 185 • Neck abscess, right pneumothorax
- 186 • Pancreatitis with retroperitoneal collection
- 187 • Sepsis
- 188 • Septic shock and acute renal failure
- 189 • Appendicitis and gangrene
- 190 • Cholangitis, septic shock and multi-organ failure (MOF)
- 191 • Ischemic gangrenous large bowel
- 192 • Brochopneumonia
- 193 • Acute cholecystitis with liver abscess and septic shock
- 194 • Necrotizing fasciitis, septic shock with amputation
- 195 • Severe Community-acquired pneumonia
- 196 • Necrotizing fasciitis
- 197 • Hip implant infection
- 198 • Severe pneumonia with respiratory failure
- 199 • *Klebsiella* septicemia with meningitis
- 200 • Retropharyngeal abscess
- 201 • Acute cholecystitis with pneumonia
- 202 • Necrotizing fasciitis with septic shock
- 203
- 204 Measured energy expenditure, actual calories received, oxygen consumption

205 and carbon dioxide production during and upon liberation from mechanical
 206 ventilation were all statistically different (Table 2). Measured energy
 207 expenditure during mechanical ventilation was 9% higher than without (Figure
 208 1) and the difference was statistically significant (Table 2). The range of
 209 PREMEE was 1299 to 3115 kilocalories and POSTMEE was 882 to 3290
 210 kilocalories (Figure 2). The actual calories received met 55% of measured
 211 energy expenditure during ventilatory support and 59% upon liberation from
 212 ventilators (Figure 1). Furthermore, 94% (n=33) of patients during mechanical
 213 ventilation and 77% (n=27) of them upon liberation from ventilator support
 214 received actual calories that were less than their measured energy expenditures.

215
 216 Mean respiratory exchange ratio (mean values of individual patient) shown in
 217 Figure 3 was higher during than upon liberation from mechanical ventilation
 218 but it was not statistically different (Table 2). The range of respiratory
 219 exchange ratios during mechanical ventilation was 0.74 to 1.32 and without
 220 ventilatory support was 0.66 to 1.22 (Figure 3)²⁰.

221
 222 The cohort showed 11% higher oxygen consumption (Figure 4) during than
 223 upon liberation from mechanical ventilation (Table 2). The minimum oxygen
 224 consumption during mechanical ventilation was 0.180 l/min and maximum
 225 was 0.478 l/min, whereas without ventilatory support the range was 0.128
 226 l/min to 0.514 l/min. Mean carbon dioxide production was 13% higher during
 227 mechanical ventilation than without ventilatory support (Table 2). Carbon
 228 dioxide production in patients on mechanical ventilation ranged from 0.184
 229 l/min to 0.406 l/min and upon liberation from mechanical ventilation was
 230 0.113 l/min to 0.365 l/min (Figure 5).

231
 232 Figure 6 illustrates substrate utilization among the cohort. Carbohydrate
 233 utilization during mechanical ventilation was 238% of lipid oxidation whereas
 234 it was 167% upon liberation from ventilator support. Minimum carbohydrate

utilization was 0.05 g/min and maximum was 0.49 g/min during mechanical ventilation and 0.00 g/min to 0.38 g/min upon liberation from ventilation (Figure 7). Minimum lipid oxidation was 0.00 g/min and maximum was 0.20 g/min during mechanical ventilation and 0.00 g/min to 0.25 g/min upon liberation from ventilation (Figure 8).

The Spearman correlation coefficients (Table 3) demonstrated strong positive relationship in which elevated oxygen production was observed with an increase in lipid utilization ($r = 0.74$) both during and upon liberation from mechanical ventilation ($r = 0.82$). Similar correlation was found in carbon dioxide production that also increased with higher lipid utilization upon liberation from mechanical ventilation ($r = 0.91$). Furthermore, the correlation was moderately strong in higher actual calories received with longer duration of mechanical ventilation support ($r = 0.55$) and length of stay ($r = 0.41$).

Discussion

Healthy people seldom realize the effort to breathe because it is a normal mechanical process and requires minimal metabolic effort in healthy individuals. Respiratory muscles including diaphragm and intercostal muscles between the ribcage are actively engaged in the ventilation mechanism and diaphragmatic fatigue contributes to respiratory failure. The positive relationship between use of various mode of mechanical ventilation including total and partial pressure support and rate of diaphragmatic atrophy has been identified among critically ill patients^{15,44} and the current study documents changes in energy expenditure when liberated from mechanical ventilation. The current cohort exhibited significant negative energy balance both during and upon liberation from mechanical ventilation. Underfeeding is common⁴ in intensive care because of conservative practice and frequent interruption by complications, procedures and examinations. A structured nutrition support protocol or algorithm could provide guidance for clinicians to prescribe nutrition support appropriately, heighten clinicians' awareness to minimize

264 negative energy balance and reduce potential cumulative energy deficit with
265 prolonged patients' length of stay.

266

267 In the present study, the absolute mass of carbohydrate utilized was higher
268 than lipids oxidized with and without mechanical ventilation, so carbohydrate
269 metabolism undoubtedly plays an important role among critically ill patients.
270 However, when considering substrate selection data collected in this
271 population, factors such as disruption in heart rate and adjustment of ventilator
272 setting should be considered as these can alter minute ventilation and
273 temporarily influence carbon dioxide production which can lead to errors.
274 Similar to high-intensity exercise ¹⁸, potentially high rates of glycolytic flux
275 and glycogenolysis during critical illness can confound standard estimates
276 based on exclusive oxidation of glucose.

277

278 The limitation of using critically ill patients in clinical trials remains difficult
279 and requires a lot of technical considerations because of the heterogeneous
280 nature of the cohort. Recruitment criteria of critically ill patients in most
281 studies are usually by location and seldom a specific disease and there are
282 clinical conditions to the formation of syndromes rather than well-defined
283 diagnosis. Moreover, patients whose disease progression warrants admission
284 to the intensive care can be in their late and more severe stages. Nonetheless,
285 increased understanding of the risk factors of selected conditions and
286 limitations of the clinical syndrome will allow appropriate patients to be
287 selected for specific trials²³.

288

289 Additional challenges and limitation in this study include variability in
290 sedation management and body mass. Firstly, sedation prescription was
291 protocol-driven and levels of sedation were similar among the cohort and
292 throughout the study; the lower level of sedation upon weaning from
293 mechanical ventilation in this study cannot therefore account for higher energy

expenditure than during ventilatory support. In terms of metabolically active muscle mass, this can directly predict energy expenditure yet could not be directly ascertained or assumed stable in this study due to the addition/removal of resuscitation fluid and/or loss of muscle mass with prolong total bed rest. Finally, duration in intensive care represents a major confounding variable given that caloric intake was positively associated with how long a patient remained on the ward. The length of stay in intensive care was longer than duration on mechanical ventilation because patients would usually be weaned from mechanical ventilation prior to transfer to general care wards (Table 1).

Conclusion

This study provides novel insight regarding the metabolic profile of critically ill patients during mechanical ventilation and in the transition towards liberation. The observed responses in patients' respiration and ventilatory cycles hold potential implications for nutritional support with a view to improved clinical outcomes. The economic benefits of accurate metabolic profiling amongst critically ill populations can bring positive impact on healthcare savings^{33,38} and should form the focus of future studies.

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